

Some Aspects of Orthomolecular Medicine*

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Nearly forty years ago, after having worked for a decade on the determination of the structure of relatively simple inorganic and organic molecules, I became interested in a protein, hemoglobin. This interest arose from the consideration of the structural origin of the sigmoid oxygen equilibrium curve (Pauling 1935). It was soon extended to include the denaturation of hemoglobin and other proteins (Mirsky and Pauling 1936) and the magnetic properties of hemoglobin and its derivatives (Pauling, Coryell, Stitt, Taylor, Dodson, and Russell 1936 to 1940). The study of magnetic properties has been especially fruitful in providing information about the nature of the bonds formed by the iron atoms in hemoglobin with the neighboring atoms of the porphyrin ring system, the globin, and attached

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molecules such as the oxygen molecule (Pauling and Coryell 1936; Coryell 1939; Coryell and Pauling 1940).

The discovery of the abnormal hemoglobins was the result of the consideration of hypothetical molecular mechanisms of the disease. In the spring of 1945 I, together with eight men from medical schools, was serving as a member of the Medical Advisory Committee of the United States government. One evening Dr. William B. Castle, Professor of Medicine in Harvard University, mentioned to the other members of the Committee the disease sickle-cell anemia, with which he had had some experience. He told about the discovery of the disease by Dr. J. B. Herrick, in 1910, and described the characteristic change in shape of the red corpuscles and the effect of oxygen in preventing the sickling and of carbon dioxide in accelerating it. I suggested that the action of carbon dioxide was to accelerate the dissociation of oxygen from oxyhemoglobin, and I pointed out that the relation of sickling to the presence of oxygen clearly indicated that the hemoglobin molecules in the red cell are involved in the phenomenon of sickling, and that the difference between sickle-cell -anemia red corpuscles and normal red corpuscles could be explained by postulating that the former contain an abnormal kind of hemoglobin, which when deoxygenated has the power of combining with itself into long rigid rods, which ^{line up side by side to form a long crystal that} twist the red cell out of shape. The opportunity to test this idea arose when Dr. Harvey A. Itano, a young physician, came to the California Institute of Technology in the fall of 1946 to work with me. In a letter to Dr. Itano before his arrival I suggested that he investigate the hemoglobin from the red cells of sickle-cell-anemia patients, in order to see whether it was different from normal adult human hemoglobin. On his arrival in Pasadena in September 1946 he began this investigation. He verified the published reports (Hahn and Gillespie, 1927) that carbonmonoxyhemoglobin, like oxyhemoglobin, prevents sickling of the red cells, and found that some other hemoglobin derivatives, including alkylisocyanide-ferrohemoglobin, ferrihemoglobin, ferrihemoglobin

azide, and ferrihemoglobin cyanide similarly prevent sickling. He developed a rapid diagnostic test for sickle-cell anemia and sickle-cell trait, based on the use of a chemical reducing agent (Itano and Pauling, 1949). Most of the properties of the hemoglobin from the blood of sickle-cell-anemia patients were found to be the same, to within the error of determination, as those of hemoglobin from normal individuals, but it was finally clearly shown, by careful measurement of electrophoretic mobility, that the blood of the patients contains nearly 100 percent of an abnormal hemoglobin, differing from normal adult human hemoglobin, and that the blood of the parents of patients contains an approximately half-and-half mixture of the abnormal hemoglobin and normal adult human hemoglobin. This electrophoretic work was carried out with the collaboration of Dr. S. J. Singer and Dr. Ibert C. Wells.

In 1949 we published a paper with the title Sickle-cell Anemia, A Molecular Disease (Pauling, Itano, Singer, and Wells 1949). In this paper we communicated our discovery that patients with the disease sickle-cell anemia have in their erythrocytes a form of hemoglobin differing from that manufactured by other people. We pointed out that the difference in molecular structure of the hemoglobin manufactured by persons suffering from this disease leads to a difference in properties of the hemoglobin molecules from those manufactured by other people, and that this difference in properties is responsible for the manifestations of the disease. The disease can properly be described as a disease of the hemoglobin molecule, rather than of the erythrocyte itself, and in consequence it may be called a molecular disease.

Later work in our laboratories in the California Institute of Technology and by other investigators elsewhere showed that the hemoglobin molecule contains four polypeptide chains, two of one kind, the alpha chains, and two of another kind, the beta chains (Rinesmith, Schroeder, and Pauling 1957; Rhinesmith, Schroeder, and Martin 1958).

It was then shown by Ingram (1957) that sickle-cell-anemia hemoglobin differs from normal hemoglobin in having one of the 146 amino-acid residues in each beta chain different from that in normal human hemoglobin, the difference being a replacement of a glutamic-acid residue in the sixth position from the amino end of the beta chain in normal adult human hemoglobin by a residue of valine. Many other abnormal forms of human hemoglobin have now been discovered, and many diseases have been recognized as diseases of the hemoglobin molecule. Other molecular diseases have also been identified. These diseases for the most part are genetic diseases, the result of a gene mutation.

The disease phenylketonuria, discovered about forty years ago by Fölling in Norway, is another example of a molecular disease. This disease involves a gene mutation such that the patient fails to manufacture molecules of an enzyme normally present in the liver, which catalyzes the oxidation of phenylalanine to tyrosine, or produces an abnormal enzyme, with greatly reduced catalytic activity. The patients are homozygotes, who have inherited the gene in double dose, usually from a heterozygotic father and a heterozygotic mother. The patients on a normal diet have in their tissues abnormally high concentrations of phenylalanine and some of its reaction products, which cause the physical and ~~the~~ mental manifestations of the disease--severe eczema, mental deficiency, and so on. The treatment that has ^{had} considerable success is to place the patients, from the age of one month or two months, on a diet of foods from which a considerable amount of phenylalanine has been removed. This decrease in the amount of phenylalanine ingested by the patients results in an approximation to the normal or optimal ^{um} concentrations of phenylalanine and its reaction products in the body fluids, and to the alleviation of the physical and mental manifestations of the disease.

Another molecular disease for which a molecular treatment is available is diabetes. This disease results from a gene abnormality such that the patient does not manufacture the proper amount of the hormone insulin. The disease can be controlled by the injection of insulin, to bring

the concentration to approximately the normal or optimum^{um} value.

Orthomolecular Medicine

Phenylketonuria involves the presence in the body of phenylalanine and its reaction products in amounts greater than normal. It is treated by reducing the intake of phenylalanine and in this way reducing the concentration of this substance and its reaction products to approximately the normal level. Diabetes involves a deficiency of insulin. It is treated by injecting insulin, and increasing the concentration to approximately the normal value. These diseases are controlled by changing the concentrations of substances that are normally present in the body.

I have reached the conclusion, through arguments summarized in the following paragraphs, that a general method of treatment of disease, which may be called orthomolecular medicine, may be found to be of great value, and may turn out often to be the best method of treatment for many patients (Pauling 1968).

Orthomolecular medicine is the preservation of health and the treatment of disease by the provision of the optimum^{um} molecular constitution of the body, especially the optimum^{um} concentration of substances that are normally present in the human body and are required for life. The adjective orthomolecular is used to express the idea of the right molecules in the right concentration.

An example of orthomolecular medicine, in addition to the two mentioned above, is the prevention of death by starvation through the provision of an adequate daily intake of carbohydrates, essential fats, proteins (including the essential amino acids), essential minerals, and vitamins. To achieve the best of health, the rate of intake of essential foods should be such as to establish and maintain the optimum concentrations of essential molecules, such as those of ascorbic acid. There is no doubt that a proper concentration of ascorbic acid is needed to provide the maximum protection against infection, and to permit the rapid healing of the wounds. I believe

that in general the treatment of disease by the use of substances, such as the vitamins, that are normally present in the human body and are required for life is to be preferred to the treatment by the use of synthetic drugs or plant products, which may have undesirable side effects.

Another example of orthomolecular medicine is the use of iodine to prevent goiter. Iodine is required by a human body, in the amount about 0.3 mg per day. In some parts of the world the food and water are deficient in this element, and in these regions goiter tends to be endemic.

The element iodine was discovered in 1811 by Courtois, in an extract of kelp. By 1820 a physician in Geneva had used tincture of iodine in the successful treatment of patients with goiter. In fact, iodine had ^{unwittingly} been used in treating and preventing goiter for some centuries, in both Europe and Asia--a folk remedy for goiter was to eat seaweed and the ashes of burned seasponge. For some years after 1820 there was much enthusiasm for the use of iodine. A French chemist, Chatin, carried out a systematic study of the iodine content of soil, water, and air in regions where goiter was endemic and in other regions, and showed that goiter ^{is} ~~was~~ associated with a deficiency of iodine in the environment. By 1831 it had been suggested (by Boussingault) that the salt should be iodized in ^{goitrous} ~~goitrous~~ regions.

The opinion of medical authorities changed, however, because of the possibility of damage from the toxicity of iodine when used in too large amounts, and the use of added iodine in the diet to control goiter remained without medical sanction for approximately one century, although many people continued to act on the widespread popular belief that iodine ^{is} ~~was~~ effective against goiter.

In 1895 it was discovered that iodine is present in the thyroid gland in far larger concentrations than in other parts of the body. An American investigator, David Marine, began the study of iodine in rela-

tion to goiter. In 1917 and 1918 he carried out a study of the effect of small doses of iodine given to school children in Akron, Ohio, and found that these small doses greatly reduced the incidence of simple goiter in the children in that goitrogenic area. Other investigators verified his results, and the use of iodine for control of goiter soon became general. Iodized salt as used in the United States contains about 1 mg of iodine per 10 grams of sodium chloride. The daily intake of iodine by human beings that is required for good health is not known with certainty, but is estimated to be about 0.3 mg per day.

Orthomolecular Treatment of Mental Disease

I believe that orthomolecular therapy may have a special value in the treatment of mental disease. The functioning of the mind is dependent on its molecular environment, the molecular structure of the brain. The presence in the brain of molecules $\overset{\text{N}}{\text{N}}$ -diethyl-D-lysergamide, mescaline, or some other schizophrenogenic substance often is associated with profound psychic effects. The phenomenon of general anesthesia also illustrates the dependence of the mind (consciousness, ephemeral memory) on its molecular environment.

The proper functioning of the mind is known to require the presence in the brain of molecules of many different substances. For example, mental disease, usually associated also with physical disease, results from a low concentration in the brain of thiamine (Vitamin B₁), nicotinic acid or nicotinamide (B₃), pyridoxine (B₆), cyanocobalamin (B₁₂), biotin (H), ~~and~~ ^{or} ascorbic acid (Vitamin C). Also, there is evidence that mental function and behavior are affected by changes in the concentration in the brain of any one of a number of other substances that normally present, such as glutamic acid, uric acid, and gamma-aminobutyric acid.

Optimized Molecular Concentrations

Several arguments may be advanced in support of the thesis that

the optimal^{um} molecular concentrations of substances normally present in the body may be different from the concentrations provided by the diet and by the gene-controlled synthetic mechanisms of the body, and also, for essential nutrilites, such as vitamins, essential amino acids, and essential fatty acids, different from the minim^{um} daily amounts required for life for the average human being or the "recommended" daily amounts suggested for good health.

One argument can be developed through consideration of the process of evolution and natural selection. The process of evolution does not necessarily result in the normal provision of optim^{um} molecular concentrations. Let us use ascorbic acid as an example. Irwin Stone (1966) has pointed out that of the mammals that have been studied in respect to their need for ascorbic acid, the only species that have lost the power to synthesize this substance and that accordingly require it in the diet are man, other primates (Rhesus monkey, Formosan long-tail monkey, ringtail or brown Capuchin monkey), the guinea pig, and an Indian fruit-eating bat (*Pteropus medius*); in addition passeriform birds, including the Red-vented Bulbul (*Pycnonotus Cafer*), some fish (trout and salmon), and some species of grasshoppers are unable to synthesize their own ascorbic acid. Presumably the loss of the gene or genes controlling the synthesis of the enzyme or enzymes involved in the conversion of glucose to ascorbic acid occurred some twenty million years ago in the common ancestor of man and other primates, and occurred independently for the guinea pig and other isolated species mentioned above, in each case in an environment such that a good supply of ascorbic acid was provided by the available food. The advantage to the mutant of being rid of the machinery for the synthesis of ascorbic acid (decrease in cell size and energy requirement, liberation of machinery for other purposes) might well be large. A disadvantage nearly as large resulting from a less than optimal supply of dietary ascorbic acid would not prevent the replacement of the earlier species by the mutant.

Hence the amount of the vitamin provided by the diet available at the time of the mutation might be less than the optimal^{umv} amount. Moreover, it is possible that the environment has changed during the last twenty million years in such a way as to provide a decreased amount of the vitamin for the average human being. Even a serious disadvantage of the changed environment would not lead to a mutation restoring the synthetic mechanism, because of the small probability of such mutations, far smaller than of those resulting in loss of function.

Individual Variation

The human race is characterized by large genetic heterogeneity. Enzyme concentrations in the tissues of different persons often differ by ²/_{the} factor of two or even a factor of ten or one hundred, as has been pointed out especially by Professor Roger J. Williams of the University of Texas. Heterozygosity in the gene for phenylketonuria halves the amount of the enzyme phenylalanine hydroxylase, and homozygosity in this gene reduces the amount of effectiveness of the enzyme by two or more orders of magnitude.

Molecular Concentrations and Rate of Reactions

The rate of an enzyme-catalysed reaction is approximately proportional to the concentration of reactant until concentrations are reached that largely saturate the enzyme. The saturating concentration is larger for a defective enzyme with decreased combining power for the substrate than for the normal enzyme. For such a defective enzyme the catalysed reaction could be made to take place at or near its normal rate by an increase in the concentration of the substrate, ~~Fig. 14~~. Moreover, an increase in concentration of an enzyme inhibitor can decrease the rate of reaction; for example, an increase in concentration of nicotinamide, with the consequent inhibition of the enzyme diphosphopyridine nucleotidase, decreases the rate of hydrolysis of diphosphopyridine nucleotide. Also, increase in concentration of a coenzyme (which might be a vitamin) increases

the amount of active enzyme formed by combination of the coenzyme and the apoenzyme, and may thus compensate for a genetic defect in the apoenzyme. Some people are of a genotype such that good health can be achieved by the intake of a far larger amount of a vitamin than is needed by other people. An example of such a genotype is provided by the disease methylmalonicaciduria. The patients with this disease are deficient in the active enzyme that catalyzes the conversion of a simple substance, methylmalonic acid, to succinic acid. It is known that cyanocobalamin (vitamin B₁₂) serves as the coenzyme for this reaction. It is found that for some patients with the disease the provision of very large amounts of vitamin B₁₂, giving concentrations about 1,000 times the normal concentration, causes the reaction to proceed at the normal rate. There is little doubt that the gene defect in these patients is one that introduces a change in an amino acid residue in the apoenzyme, which combines with vitamin B₁₂ to form the active enzyme. This change is of such a nature as to decrease the combining power of the apoenzyme with the coenzyme, vitamin B₁₂. The large increase in the concentration of vitamin B₁₂ serves to shift the chemical equilibrium between apoenzyme, coenzyme, and active enzyme in such a way that the amount of the active enzyme becomes normal.

Evidence from Microbiological Genetics

Many mutant microorganisms are known to require, as a supplement to the medium on which they are grown, a substance that is synthesized by the corresponding wild-type organism. An example is the "pyridoxineless" mutant of *Neurospora Sitophila* reported by G. W. Beadle and E. L. Tatum in their first *Neurospora* paper, published in the Proceedings of the National Academy of Sciences in 1941. They found the rate of growth of this mutant on their standard medium to be only nine percent of that of the wild type. When pyridoxine (Vitamin B₆) is added to the medium, the rate of growth at first increases nearly linearly with the

concentration of the added pyridoxine, and then the growth-rate curve bends rather sharply, and continues to increase with a much smaller slope. ~~Fig. 27~~. The region of concentrations in which the growth increases rapidly with increase in concentration may be considered to be the region of vitamin deficiency, and the concentration at which the curve changes to much smaller slope may be considered to correspond to an "adequate" or "recommended" amount of the vitamin, in that the growth rate of the mutant is then only a few percent less than that of the wild strain, and the amount of the vitamin would have to be increased three-fold to make up the difference.

Increasing the concentration of the growth substance to thirty-five times the "adequate" concentration for the mutant causes an increase in growth rate by about twenty-five percent. The growth rate of the mutant is then ten percent greater than that of the wild type. An increase in growth rate or in some other function of magnitude twenty-five percent or ten percent might under some circumstances be of great value, and might mean the difference between life and death or between good health and poor health, either physical or mental. Especially if the growth substance is non-toxic and free from side reactions, its therapeutic use in large amounts might well be justified.

Ascorbic acid, for example, is non-toxic for all or almost all human beings. It is required for life in amounts of a few milligrams per day. The ingestion of large amounts, three or five grams per day, seems to improve the general health of human beings, and to provide greater resistance to colds and other infectious diseases. I believe that it is likely that the ^{optimal} intake of ascorbic acid is far greater than the "approved" or "recommended" intake, and that a significant improvement in the health of human beings could be achieved by approximating this ^{optimal} intake.

Orthomolecular Psychiatry

The functioning of the brain is more sensitively dependent on the rate of chemical reaction ^{than} than the functioning of other organs and tissues.

I believe that mental disease is for the most part caused by abnormal molecular concentrations of essential substances. The operation of chance in the selection, for the child, of half of the complement of genes of the father and mother leads to bad as well as to good genotypes, and the selection of foods (and drugs) in a world that is undergoing rapid scientific and technological change may often be far from the best. Significant improvement in the mental health of many persons, especially those with borderline or mild mental illness or mental retardation, might be achieved by the provision of the optimal^{um} molecular concentrations of substances normally present in the human body, especially those that are not toxic or have low toxicity.

Among these substances, the essential nutrilites may be the most worthy of extensive research and more thorough clinical trial than they have yet received.

Nicotinic acid, when its use was introduced, cured hundreds of thousands of pellagra patients of their psychoses, as well as of the physical manifestations of their disease. For this purpose only small doses are required; the recommended daily allowance (U. S. National Research Council) is twelve milligrams per day. In 1940 Streitwieser and his associates reported some success in the treatment of severe depression and other forms of mental disease by use of large doses of nicotinic acid, three grams or more per day. Other investigators, especially A. Hoffer of Saskatchewan and H. Osmond of New York, have advocated and used nicotinic acid in large doses for the treatment of schizophrenia. The dosage recommended by Hoffer is three grams per day, or more, up to eighteen grams per day, as determined by the response of the patient, of either nicotinic acid or nicotinamide, together with four grams per day of ascorbic acid. Nicotinic acid and nicotinamide are non-toxic (LD₅₀ not known for humans, but probably over 200 grams), and their side effects, even in continued massive doses, seem not to be commonly serious. The advantages of nicotinic acid therapy have been summarized by Osmond and Hoffer (The Lancet 10 Feb.

1962, 316) in the following words: "Niacin (nicotinic acid) has some though not all the qualities of an ideal treatment: it is safe, cheap (less than one cent per gram), and easy to administer, and it uses a known pharmaceutical substance which can be taken for years on end if necessary. . . It does not seem to affect the more chronic illnesses, and even in acute illnesses its action is often less dramatic than that of some of the phenothiazines. Its protective qualities, continuing long after patients have stopped taking it, are puzzling. . . It has been proved to reduce the level of cholesterol in the blood. It seems to benefit some deliria not obviously associated with vitamin lack, and is claimed to improve many cases of intractable rheumatism. In our view, it is a useful adjunct in the treatment of schizophrenia, both for acute cases and to reduce the chance of relapses."

I believe that the study of the functioning of the brain in its relation to the concentrations and intake of the vitamins, essential amino acids, and other substances normally present in the brain constitutes a field of research in which much more work needs to be done. Biochemical and genetic arguments support the idea that orthomolecular therapy, the provision for the individual human being of the optimal^{um} concentrations of important normal constituents of the human body, may be the preferred treatment for many patients, especially those with mild mental retardation or mild psychosis. I suggest that this therapy, to be successful, should involve the thorough study of the individual, and continued attention to him, such as is customary in psychoanalysis but not in conventional chemotherapy. There is the possibility that analysis of body fluids and tests of the ability of the individual to utilize essential substances may indicate the types of orthomolecular therapy that would be most likely to be effective for the patient.

It is my opinion that for those patients for whom it is effective the control of mental disease by varying the concentrations in the brain of non-toxic substances that are normally present, such as nicotinic acid and

ascorbic acid, is to be preferred to other means of therapy that involve a greater insult to the body and mind (see Hawkins and Pauling 1973).

Ascorbic Acid and the Common Cold

The use of L-ascorbic acid, vitamin C, in preventing the serious deficiency disease scurvy has long been recognized. During recent years increasing recognition has been given also to ascorbic acid, ingested in the proper amounts, as an effective means of decreasing the incidence of infectious diseases, especially the common cold. This use may be one of the most important examples of orthomolecular medicine.

Scurvy has been known for hundreds of years. Until about a century ago the disease was very common among sailors on board ships taking long voyages, and also among soldiers in an army in campaign, in communities in times of scarcity of food, in cities under siege, and in prisons and work houses.

The onset of scurvy is marked by a failure of strength, including restlessness and rapid exhaustion on making effort. The patient complains of pains in the muscles, caused by hemorrhages of large size that penetrate the muscles and other tissues, giving him the appearance of being extensively bruised. He is mentally depressed, and his face looks haggard. His gums ulcerate, his teeth drop out, and his breath is fetid. His joints loose their integrity. Death then results from profound exhaustion, diarrhea, and pulmonary and kidney troubles.

Four hundred years ago the English Admiral Sir John Hawkins recognized that sailors with scurvy recovered as soon as they got access to a supply of succulent plants, and that scurvy could be prevented by carrying on the ship fruits of the orange type, including oranges and lemons. In 1795 the British Admiralty ordered that a daily ration of lemon juice (called lime juice) be given to the sailors, and scurvy disappeared from the British Navy. In 1865 the British Board of Trade passed a similar lime-juice regulation for the Merchant Marine. At the present time

scurvy, complicated by other deficiency diseases, is found in populations that are ravaged by starvation and severe malnutrition, usually as a result of poverty, and occasionally in infants six to eighteen months old who are fed a formula without vitamin supplement, and in middle-aged or elderly bachelors or widowers who for convenience ingest an unsatisfactory diet, deficient in vitamins.

The substance L-ascorbic acid was discovered in 1928 by Albert Szent-Györgyi, who isolated it from cabbages and other vegetables and the adrenal glands of animals. He soon found that Hungarian paprika contains large amounts of the substance, and in 1932 this substance was shown to be vitamin C, the antiscorbutic principle, by Svirbely and Szent-Györgyi and by Waugh and King.

An intake of ascorbic acid of 5 to 10 milligrams per day is enough to protect almost all people against scurvy. This fact has caused the Food and Nutrition Board of the United States National Academy of Sciences to recommend a daily allowance of 60 milligrams for an adult male. The corresponding British Board recommends only 30 milligrams per day.

There is the possibility, however, that a much larger intake of ascorbic acid would lead to improved general health, including increased resistance to infectious disease. There is a popular belief that ascorbic acid provides protection against the common cold. Szent-Györgyi himself has recently made the following statement: "As to ascorbic acid, right from the beginning I felt that the medical profession misled the public. If you don't take ascorbic acid with your food you get scurvy, so the medical profession said that if you don't get scurvy you are all right. I think that this is a very grave error. Scurvy is not the first sign of the deficiency but a premortal syndrome, and for full health you need much more, very much more. I am taking, myself, about 1 g a day. This does not mean that this is really the optimum dose because we do not know what full health really means and how much ascorbic acid you need for it. What I can tell

you is that one can take any amount of ascorbic acid without the least danger. "

The United States Food and Nutrition Board has stated that there is no convincing evidence that increased intake of ascorbic acid, above the amount 60 mg per day, leads to improvement in health. A similar statement is made by almost all authorities in the fields of nutrition and medicine. In particular, it is repeatedly stated by these authorities that there is no convincing evidence that ascorbic acid has any value in decreasing the incidence or severity of the common cold or in providing similar protection against other infectious diseases.

A few scientists and physicians have, however, opposed the official opinion. My attention was called to this situation in April 1966, when I received a letter from Irwin Stone, a biochemist in Staten Island, New York, in which he recommended that I follow his regime of increased ascorbic-acid intake, to achieve an improvement in my health. My own experience during the years since that time confirmed the statements made by Stone about the value of ascorbic acid in providing protection against the common cold. I became aware of the striking contradiction between the statements of most authorities and the popular belief about the value of ascorbic acid, and I decided to make a search of the medical literature, in order to find out what facts had been revealed by carefully controlled studies of ascorbic acid in relation to the common cold and other infectious diseases. I found, as has been described in my book Vitamin C and the Common Cold, published in December 1970, that there exist in the medical literature reports of a number of carefully controlled studies, in which the average incidence and severity of the common cold in a group of subjects regularly receiving a daily amount of ascorbic acid has been compared with the values for a group of subjects selected at random from the same population and receiving an inactive substance (a placebo), with all of the subjects exposed to cold viruses in the ordinary way, through contact with other people. As is described later in this article, several of these careful investigations have

given results with statistical significance, showing that ascorbic acid does have value in decreasing the incidence and the severity of the common cold, and that the effectiveness of the ascorbic acid increases with increase in the amount taken per day. On the other hand, no controlled study carried out under these conditions have given results that rule out, with statistical significance, the amount of protective effect of ascorbic acid described below. It is my opinion that there is no doubt that ascorbic acid, taken in the proper amount, has value in decreasing both the incidence of the common cold and the severity of individual colds. There is also evidence that ascorbic acid has value in providing protection against other infectious diseases.

Evolution and the Need for Ascorbic Acid

In 1966 Irwin Stone published some arguments to support his conclusion that most human beings suffer from a deficiency of ascorbic acid, not great enough to cause manifest symptoms of scurvy, but great enough to have a significant effect in a decrease in wellbeing. He suggested that most human beings could be described as suffering from hypoascorbemia, a genetic disease resulting from the inability of human beings to synthesize ascorbic acid, and from a deficiency in the supply of ascorbic acid provided by the food that they ingest. The food normally ingested by people in Europe and the United States is thought to provide an average of 30 mg to 50 mg per day, approximately the daily amounts recommended by the official Food and Nutrition Boards. Stone contends that the optimal^{um} amounts, leading to better health, are 20 to 100 times as great, that is, one gram (1,000 mg) per day or more.

One argument advanced by Stone is the rate of synthesis of ascorbic acid by the rat, which has the power to synthesize this substance, and does not depend on a supply of ascorbic acid in its food. It has been observed that rats under ordinary circumstances (not under stress) synthesize an amount of ascorbic acid corresponding, on a weight basis, for a

70-kilogram man to 2 g to 4 g per day, and that rats under stress synthesize a much larger amount. Also, the housefly synthesizes ascorbic acid at the rate 10 g per day per 70 kg.

In 1949 Bourne pointed out that the gorilla obtains about 4.5 g per day in his food (bamboo shoots and other green plants), corresponding to about 2 g per day for man. A somewhat similar argument was developed by me in 1970, based upon the amounts of various vitamins in raw natural plant foods. It is known that microorganisms, such as bacteria, yeasts, and molds, have greater power than man of synthesizing the substances that they need. These microorganisms are able to synthesize almost all of the vitamins, as well as the amino acids, whereas man must obtain from his food a supply of about a dozen vitamins and eight amino acids in order to live. Other animals are like man in requiring the various vitamins in their food. Every vertebrate that has been studied in this respect requires thiamine (vitamin B₁), riboflavin (vitamin B₂), and nicotinic acid (the anti-pellagra factor) in its food. We may consider the epoch, early in the history of life on earth, when the early animal species from which present-day birds and mammals have evolved populated a part of the earth. We assume that the animals of this species nourished themselves by eating plants, possibly together with other food. Nearly all plants contain thiamine, and accordingly the animals would have in their bodies the thiamine that they had ingested with the foods that they had eaten, as well as the thiamine that they themselves synthesized by use of their own synthetic mechanism. Let us assume that a mutant animal appeared in the population, which, as the result of action of some mutagenic agent, had lost the biochemical machinery that still permitted the other animals of the species to manufacture thiamine from other substances. The amount of thiamine provided by the ingestion of food would suffice to keep the mutant well nourished, essentially as well nourished as the unmutated animals. The mutant would accordingly have an advantage over the unmutated animals, in that it would be liberated of the burden of the machinery for manufacturing its own thiamine. As a result, the mutant would be able to have more offspring than the other animals in the population. It would pass its advantage-

ously mutated gene along to some of its offspring, and they too would have more than the average number of offspring. In the course of time this advantage, of not having to do the work of manufacturing thiamine or to carry within itself the machinery for this manufacture, would permit the mutant type to replace the original type.

The fact that all animal species require thiamine, riboflavin, and nicotinic acid as vitamins strongly indicates, according to this argument, that the amounts of these vitamins in the food available in the early period of vertebrate evolution were sufficient to supply the needs of the animals for these vitamins.

I made a study of 110 raw natural plant foods for which information about vitamin content was available, referring the vitamin content in each case to the amount of food giving 2500 kilocalories of food energy, a day's supply for a man. The average amounts of vitamins in these 110 raw natural plant foods came out 5.0 mg for thiamine, 5.4 mg for riboflavin, and 41 mg for nicotinic acid. These amounts are 3.8, 3.6, and 2.5 times, respectively, the recommended daily allowances, as set by the United States Food and Nutrition Board. These three numbers indicate that the recommended daily allowances of these three vitamins are reasonable, in that they are smaller than the amounts available in plant food, which accordingly, by the foregoing argument about evolution, would have permitted the mutations involving loss of the ability to synthesize the substances to take place.

The situation with ascorbic acid is, however, quite different. In the first place, only a few animals require ascorbic acid as a vitamin; almost all animals are able to synthesize the substance, and do not require that it be ingested with their food. We now ask why most species of animals continue to carry the burden of the machinery for manufacturing their own ascorbic acid. The answer surely is that the amount of ascorbic acid available in the diet of these animals and of their ancestral species has never been great enough to permit the ability of manufacturing their own ascorbic acid

to be given up.

The average amount of ascorbic acid in the 110 raw natural plant foods investigated turned out to be 2.3 grams, about 40 times the recommended daily allowance for a 70-kilogram man. This amount, which presumably was available to ancestors of most animal species, was not sufficient to permit the mutation to take place; accordingly it probably can be considered to be a minimum value of the optimum daily requirement for a representative 70-kilogram animal.

Some plants contain more ascorbic acid, per 2500 kilocalories of food energy, than others. The average for the 14 plants containing the largest amount of ascorbic acid is 10 grams. It seems likely that at some time in the past, about 25 million years ago, the common ancestor of man and the other primates was living in an environment where the available food contained this much ascorbic acid, and that under these conditions it was advantageous for the mechanism of synthesis of the substance to be given up.

Since then man has expanded his territorial range into areas where the food supply is deficient in ascorbic acid. He may have developed some mechanisms, such as tubular reabsorption in the kidney, to conserve ascorbic acid; but, as pointed out by Irwin Stone, it is likely also that most human beings would be improved in health by ingesting more of this valuable substance than is provided by the ordinary food supply. The loss of ascorbic acid in foods resulting from modern methods of processing and storage and from changes in the diet may have exacerbated the hypoascorbemia for many populations.

The conclusion that the optimum intake of human beings for weight 70 kg lies between about 2 g per day and about 10 g per day is not to be interpreted as applying to every human being. In 1967 Roger J. Williams and Gary Deason published results of studies made by them of the rate of growth of guinea pigs as a function of the amount of ascorbic acid provided to them. They found that the requirements of individual guinea pigs varied over a

20-fold range, and concluded that, inasmuch as human beings are probably more heterogeneous genetically than the guinea pigs used in their studies, the requirements for individual human beings might well vary over a more than 20-fold range. The conclusion that I have reached, and presented in my book Vitamin C and the Common Cold, is that for some people a daily intake of 250 mg of ascorbic acid, or even less, may suffice to provide optimal health; for many people a larger intake, between 1 g and 2 g per day, is needed, and for others even more. A good measure of the amount of ascorbic acid required by an individual is, in my opinion, provided by his resistance to the viruses of the common cold. A daily intake that protects essentially completely from the common cold (no more than one cold per year) may be considered to be approximately the amount that he needs.

Evidence about Ascorbic Acid and the Common Cold

Several careful studies of ascorbic acid and the common cold have been carried out, in which regular daily amounts of ascorbic acid were ingested by one group of subjects selected at random from a population, and tablets of an inactive substance, a placebo, were provided to another group of subjects from the same population. The subjects were exposed to cold viruses in the ordinary way, through contact with other people. Most of the studies described below were double-blind, with neither the subjects nor the physicians who kept the records knowing which of the subjects received the ascorbic acid and which received the placebo. The results were then subjected to statistical analysis.

I shall discuss in some detail ^{several} ~~the~~ investigations, ^{beginning with} one carried out by Dr. G. Ritzel, a physician with the Medical Service of the School District of the city of Basel, Switzerland, ^{another} ~~the second~~ by S. S. Charleston and K. M. Clegg of the Department of Food Science of the University of Strathclyde, Glasgow, and ~~the~~ ^{the} third by Drs. Cowan, Diehl, and Baker, physicians connected with the School of Medicine of the University of Minnesota.

The study carried out by Ritzel, reported in 1961, was made with

279 schoolboys, 15 to 17 years old, in a ski resort, during two periods of five to seven days. The conditions were such that the incidence of colds during these short periods was large enough (approximately 20 percent) to permit results with statistical significance to be obtained. The subjects had similar nutrition during the period of the study. The tablets of ascorbic acid (1000 mg) or placebo were distributed every morning and were taken by the subjects under observation such that the possibility of interchange of tablets was eliminated. The subjects were examined daily as to symptoms of colds and other infections. The records were largely on the basis of subjective symptoms, partially supported by objective observations (measurement of body temperature, inspection of the respiratory organs, auscultation of the lungs). Persons who showed cold symptoms on the first day were excluded from the investigation.

After the completion of the investigation a completely independent group of professional people was provided with the identification numbers for the ascorbic-acid tablets and placebo tablets, and this group carried out the statistical evaluation of the observations.

The number of colds for the 140 persons in the placebo group was 31, and that for the 139 persons in the ascorbic-acid group was 17. There was accordingly observed a decrease in the incidence of colds of the ascorbic-acid group, as compared with the placebo group, of 45 percent.

This decrease in incidence is statistically significant, at the level $P(\text{one-tailed})$ less than 0.02. This result means that the probability that a decrease in incidence as great as this, or greater, and in this direction (protective effect of ascorbic acid), would be observed in the two groups from a uniform population, with ascorbic acid and placebo having the same effect, only in two percent of a large number of similar tests. Hence the observation of a protective effect by ascorbic acid, decreasing the incidence of colds, is reliable at the 98-percent level of confidence.

In applying statistical analysis to this study and other studies I have calculated the value of $P(\text{one-tailed})$, rather than $P(\text{two-tailed})$, be-

cause the question under dispute is whether or not ascorbic acid has greater protective power than a placebo; no one contends that the placebo would have greater protective power than ascorbic acid. The statements made by me, as the result of my own statistical analysis, agree with those made by Ritzel, based on statistical analysis made by a team of professionals, with the difference that my statements refer to $P(\text{one-tailed})$, rather than $P(\text{two-tailed})$.

The severity of individual colds was observed by Ritzel in two ways: first, by recording the average number of days of illness per cold, and second, by recording the total number of individual symptoms per cold (as recorded each day). The severity of individual colds was found to be 29 percent less for the ascorbic-acid group than for the placebo group as measured by the average number of days of illness per cold, and 36 percent less as measured by the number of individual symptoms recorded per cold. Each of these decreases has statistical significance at the level $P(\text{one-tailed})$ less than 0.05.

A third quantity, which may be taken to represent the total protective effect of ascorbic acid, is the integrated morbidity, defined as the product of the incidence of colds and the severity of individual colds. In the Ritzel study the integrated morbidity was found to be 61 percent less for the ascorbic-acid group than for the placebo group as measured by the average number of days of illness per subject in the group, and 64 percent less as measured by the average number of individual symptoms per person in the group. Each of these observations is statistically significant at the level $P(\text{one-tailed})$ less than 0.005. This investigator, Ritzel, has accordingly reported, in his carefully prosecuted double-blind study of 279 subjects, that the administration of 1,000 mg per day of ascorbic acid, in comparison with a placebo, leads to a decrease in incidence, severity, and integrated morbidity of the common cold, with high statistical significance. The integrated morbidity is correlated with the incidence and severity; accordingly

the statistical significance of the investigation as a whole can be taken to be rejection of the null hypothesis that ascorbic acid has the same value as the placebo at the level $P(\text{one-tailed})$ less than $\overset{0.005}{0.01}$; that is, at the confidence level $99.\overset{5}{\text{A}}$ percent.

The second study, by Charleston and Clegg (1972), was also carried out with 1000 mg of ascorbic acid per day. Of the 90 subjects (staff and students of the University of Strathelyde), 47 received ascorbic acid and 43 received the placebo. In the 15 weeks of the study the ascorbic-acid subjects had 44 colds and the placebo subjects had 80 colds. The decrease in incidence was accordingly 49 percent ($P \leq 0.002$), as compared with Ritzel's 45 percent. The average duration of colds (3.5 vs. 4.2 days) was also decreased, by 17 percent, so that the integrated morbidity was 58 percent less for the ascorbic-acid subjects than for the placebo subjects, as compared with Ritzel's 61 ^{and} 64 percent. These two studies agree well with one another in indicating about half as much illness with an intake of 1000 mg of ascorbic acid per day as with a placebo.

Another very careful study of ascorbic acid and the common cold was reported in 1942 by Cowan, Diehl, and Baker. Their principal work was done during the winter of 1939-1940, over a period of 28 weeks. The subjects were all students in the University of Minnesota who volunteered to participate in the study because they felt that they were particularly susceptible to colds. Persons whose difficulty seemed to be due primarily to chronic sinusitis or allergic rhinitis, as shown by examination of the nose and throat and consideration of symptoms of allergy, were excluded from the study. The subjects were assigned alternately and without selection to an experimental group and a control group. The subjects in the control group were treated exactly like those in the experimental group, except they received a placebo instead of the ascorbic acid. The subjects were instructed to report to the health service whenever a cold developed, so that report cards could be filled in by a physician. This study was a double-blind

one, with neither the subjects nor the physicians knowing which group a subject was in. There were 183 subjects in the ascorbic-acid group, who received an average of 180 mg per day of ascorbic acid during the 28-week period, and 155 subjects in the placebo group.

The amount of ascorbic acid used in this study, 180 mg per day, is a little less than one-fifth of the amount used by Ritzel and by Charleston and Clegg. The effects are also somewhat smaller. The incidence of colds was 14 percent less for the ascorbic-acid group than for the placebo group, with $P(\text{one-tailed})$ less than 0.02; the severity (average days of illness per cold) was 21 percent less, with $P(\text{one-tailed})$ less than 0.02; and the integrated morbidity (average days of illness per person) was 31 percent less, with $P(\text{one-tailed})$ less than 0.02.

A very important study was reported in 1972 by Anderson, Reid, and Beaton of the University of Toronto Medical School. They gave 1 g per day of ascorbic acid (plus 3 g per day for three days when a cold began) to half of 818 subjects, and a placebo to the other half. The amount of respiratory illness was 30 percent less for the ascorbic-acid subjects than for the placebo subjects, significant at the level $P(\text{one-tailed})$ less than 0.002. The amount of illness other than respiratory was 40 percent less.

Three other studies were reported in August 1973 at the symposium on vitamin C and the common cold held at Stanford University. Dr J. L. Coulehan of Ganado, Arizona reported on a study made with 635 students in an Indian school, half of whom received ascorbic acid (1 g per day for the younger students, 2 g per day for the older) and the other half a placebo. The younger ascorbic-acid group had 29 percent less respiratory illness and the older ascorbic-acid group 36 percent less than their placebo counterparts. Dr R. H. Colby of Stockton State College, New Jersey, reported the results for 67 students, half of whom received 1 g of ascorbic acid and the other half a placebo. The amount of illness was 18 percent less for the ascorbic-acid group than for the placebo group. Also, Dr T. C. Chalmers reported on a study carried out by him and Dr T. R. Karlowski in Bethesda, Maryland, with 190 subjects, half of whom received 3 g per day of ascorbic acid and the others a placebo. The decreased amount of illness for the ascorbic-